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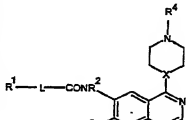
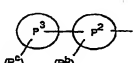
[Continued on next page]

(54) Title: ISOQUINOLINE AND QUINAZOLINE DERIVATIVES HAVING A COMBINED 5HT1A, 5HT1B AND 5HT1D RECEPTOR ACTIVITY



(I)

(i)



(ii)

(57) Abstract: The invention relates to novel isoquinoline and quinazoline derivatives of formula (I) having $5HT_{1A}$, $5HT_{1B}$ and $5HT_{1D}$ receptor affinity, processes for their preparation, to compositions containing them and to their use in the treatment of various disorders in which R^1 is selected from a group of formula (i) where P^1 is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, a benzofused heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a pyridofused heterocyclic ring containing 1 to 3 nitrogen atoms; R^a is halogen, C_{1-6}alkyl, C_{3-6}cycloyalkyl, CF_3, C_{1-6}alkoxy, OCF_3, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, COC_{1-6}alkyl, CO_2R^5, SO_2R^5, NR^5R^6, $CONR^5R^6$, and $SO_2NR^5R^6$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl; n is 0,1,2 or 3; or group of formula (ii) in which P^2 and P^3 are independently as defined for P^1 above; R^b and R^c are independently as defined for R^a above; p and q are independently as defined for n above; L is a single bond or NH; R^2 is hydrogen or together with the group R^3 forms a further group -CH = CH- or $(CR^7R^8)_2$ where R^7 and R^8 are independently hydrogen or C_{1-6}alkyl; R^3 is hydrogen or together with R^2 forms a further group as defined above; Y is N or CH; X is N or CH; R^4 is hydrogen or C_{1-6}alkyl.

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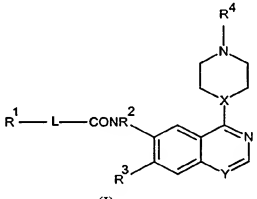
ISOQUINOLINE AND QUINAZOLINE DERIVATIVES HAVING A COMBINED 5HT1A, 5HT1B AND 5HT1D RECEPTOR ACTIVITY

The present invention relates to novel isoquinoline and quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them and to their use in the treatment of various disorders.

WO 98/50358, WO 98/50346, WO 98/47868, WO 98/47885, WO 98/50543 and WO 99/31086 all disclose a series of novel compounds which are claimed to possess combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor affinity and which are useful in the treatment of various CNS disorders. WO 97/36867 and WO 98/14433 both disclose a series of lactam derivatives that are claimed to be selective agonist or antagonists of one or both of 5-HT_{1A} and 5-HT_{1D} receptors.

A structurally distinct class of compounds have now been found that also exhibit combined 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptor affinity. It is expected that such compounds will be useful for the treatment and prophylaxis of various disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which R^1 is selected from a group of formula (i) or (ii);

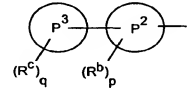
Group of formula (i)

(i)

where P^1 is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, a benzofused heterocyclic ring

containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a pyridofused heterocyclic ring containing 1 to 3 nitrogen atoms;
R^a is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, CF_3, C_{1-6}alkoxy, OCF_3, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, COC_{1-6}alkyl, CO_2R^5, SO_2R^5, NR^5R^6, $CONR^5R^6$, and $SO_2NR^5R^6$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl;
n is 0, 1, 2 or 3;

Group of formula (ii)



(ii)

in which P^2 and P^3 are independently as defined for P^1 above;
R^b and R^c are independently as defined for R^a above;
p and q are independently as defined for n above;

L is a single bond or NH;
R^2 is hydrogen or together with the group R^3 forms a further group -CH = CH- or $-(CR^7R^8)_2-$ where R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;
R^3 is hydrogen or together with R^2 forms a further group as defined above;
Y is N or CH;
X is N or CH;
R^4 is hydrogen or C_{1-6}alkyl.

C_{1-6}alkyl groups whether alone or as part of another group may be straight chain or branched. Where used herein the term naphthyl is intended, unless otherwise stated, to denote both naphth-1-yl and naphth-2-yl groups. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

Within the definition of R^1 formula (i)

When P^1 is a 5 or 6 membered heteroaryl ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl and pyrazinyl. Where used herein the term "benzofused heterocyclic ring" is used to describe both 6,5 and 6,6 benzofused heteroaryl rings and benzofused non aryl heterocyclic rings. Suitable

examples of benzofused heteroaryl rings include indolyl, benzofuryl, benzothienyl, quinolinyl and isoquinolinyl. Benzofused non aryl heterocyclic rings may be substituted by an oxo group. Suitable examples of benzofused non aryl heterocyclic rings include indolinyl, benzoxazinyl and benzoxazinonyl. When P^1 is pyridofused heterocyclic ring a preferred example is pyrazolopyridinyl. The rings defined for P^1 can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom.

Preferably P^1 is phenyl, naphthyl, quinolinyl, isoquinolinyl or a 5 or 6 membered heteroaryl ring such as pyridyl, oxazolyl, furyl, thiazolyl, imidazolyl, oxazolyl or pyrazolyl.

When n is not 0, R^a is preferably halogen (particularly fluorine, chlorine or bromine), a C_{1-6}alkyl group (particularly methyl, ethyl, isopropyl or t-butyl), CF_3, cyano, C_{1-6}alkoxy group (particularly methoxy or ethoxy) or SO_2R^5 where R^5 is methyl. When n is 2 or 3 the groups R^a may be the same or different. Preferably n is 1 or 2.

Within the definition of R^1 formula (ii)

Suitable P^2 and P^3 groups include those listed for P^1 above. The rings defined for P^2 and P^3 can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen atom. Preferably P^2 is phenyl, naphthyl or a 5 or 6 membered heteroaryl ring such as thienyl, thiazolyl, oxazolyl and most preferably pyrazolyl. Preferably P^3 is pyridyl or most preferably phenyl.

When p and/or q is not 0, R^b and R^c are preferably halogen (particularly fluorine, chlorine or bromine), a C_{1-6}alkyl group (particularly methyl, ethyl, isopropyl or t-butyl), CF_3, cyano, C_{1-6}alkoxy group (particularly methoxy or ethoxy). When p and/or q are 2 or 3 the groups R^b and R^c respectively can be the same or different. Preferably p is 0 or 1. Preferably q is 0, 1 or 2.

When L is NH, R^1 is preferably a group of formula (i). Preferably L is a single bond.

When R^2 together with a group R^3 forms a group $-(CR^7R^8)_2-$ both of the groups R^7 and R^8 are preferably hydrogen.

Preferably Y is CH.

Preferably X is N.

Preferably R^4 is hydrogen or a methyl group.

Preferred compounds of this invention are examples E1 - E89 (as described below) or a pharmaceutically acceptable salt thereof. Particularly preferred compounds according to this invention are:

2,3-Dihydro-1-(5-methyl-1-phenylpyrazol-4-yl carbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline,
1-(2-Fluorobenzoyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline,
1-[1-(4-cyanophenyl)-5-ethylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,
1-[1-(4-cyanophenyl)-5-methylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,
2,3-Dihydro-1-(4-ethyl-2-methyloxazol-5-ylcarbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline
or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

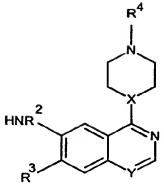
Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises:

(a) when L is single bond, coupling a compound of formula (II):

(II)

in which R^1 is as defined in formula (I) and A is an activated carboxylic acid group with a compound of formula (III);



(III)

in which R^2, R^3, R^4, X and Y are as defined in formula (I); or

(b) where L is NH, coupling a compound of formula (IV)

(IV)

in which R^1 is as defined in formula (I) and B is either -N=C=O or is NH_2 in the presence an appropriate urea forming agent, with a compound of formula (III) as defined above;

and optionally thereafter for either process (a) or (b):

- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

For process (a) suitable activated carboxylic acid groups include acyl chlorides or acyl bromides. Activated compounds of formula (II) can also be prepared by reaction of the corresponding carboxylic acid with a coupling agent such as carbonyldiimidazole dicyclohexylcarbodiimide, or diphenylphosphorylazide. Compounds of formulae (II) and (III) are typically reacted together in an inert solvent such as dichloromethane or dimethylformamide at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine. Compounds of formula (I) may also be prepared by reaction of compounds of formula (II), where A is a carboxylic ester, with compounds of formula (III) in the presence of trimethylaluminium at ambient or elevated temperature in an inert solvent such as toluene.

For process (b) in which B is -N=C=O the reaction is conveniently effected in an organic solvent such as dichloromethane. For process (b) in which B is NH_2 suitable urea forming agents are carbonyl diimidazole, triphosgene and phosgene, and the reaction is carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Intermediate compounds of formula (II), (III) and (IV) are commercially available, can be prepared using methods described herein or by analogous methods thereto or using standard procedures known in the art.

The involvement of serotonin receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

Serotonin (5-hydroxytryptamine; 5-HT) receptors have been implicated in a number of pharmacological effects including mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

Ligands with high affinity for the 5-HT_1 receptors are well recognised as having therapeutic utility for the treatment of the above conditions. For example: WO 95/31988 refers to the use of a 5-HT_{1D} receptor antagonist in conjunction with a 5-HT_{1A} receptor antagonist to treat CNS, endocrine and GI disorders; K. Rasmussen (Annual Reports in Medicinal Chemistry, (1995) 30, 1) describes the utility of 5-HT_{1A} receptor agonists and

partial agonists in the treatment of various CNS disorders; P. Trouillas (Progress in Brain Research, C.I. de Zeeuw, P. Stara and J. Voogd, Eds. 1997, 144, 589) and G. Maura (J. Neurochemistry, 1996, 66, 202) propose that administration of agonist ligands selective for the 5-HT_{1A} receptor or for both 5-HT_{1A} and 5-HT_{1D} receptors should provide effective treatment for human cerebellar ataxias.

The present invention also provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment of the aforementioned disorders. In particular, the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt for use in the treatment or prophylaxis of depression.

In a further aspect the present invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of disorders (particularly the aforementioned) in which a ligand with affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is beneficial.

In a yet further aspect the invention provides a method of treating diseases or disorders (particularly the aforementioned disorders) in which a ligand with affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is beneficial which comprises administering a safe and therapeutically effective amount to a patient in need thereof of compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, a selective serotonin reuptake inhibitor (SSRI) anti-depressant.

The affinities of the compounds of this invention for the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors can be determined by the following radioligand binding assay. HEK 293 cells expressing 5-HT_{1A} receptors (4 x 10^7/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. CHO cells expressing 5-HT_{1B} receptors (4 x 10^7 cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT_{1D} receptors (0.563 x 10^8/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4 nM) for 5-$HT_{1B/1D}$ receptors and [^{3}H]-8-OH DPAT (1 nM) for 5-HT_{1A} receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

All examples were tested in accordance with this radioligand binding assay and were found to have a pKi of greater than 7.5 at 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors.

The selectivity of the compounds of this invention for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors can be determined using binding assay methods which are well known to those skilled in the art. All examples tested were found to have a greater than 20-fold selectivity over other binding sites within the CNS, in particular, other 5-HT receptor sub-types and dopaminergic receptors. Particularly preferred examples were found to have a greater than 100 fold selectivity over other binding sites.

The intrinsic activity of the compounds of this invention can be determined according to the following procedure. HEK293 cell membranes stably expressing human 5-HT_{1A} receptors and CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1 ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 10 μl of [^{35}S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines zero intrinsic efficacy). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). Compounds of formula (I) which have low intrinsic activity in the [^{35}S]GTPγS functional assay are more likely to be antagonists *in vivo*. As disclosed in WO 95/31988, the simultaneous antagonism of pre-synaptic 5-$HT_{1A/1B/1D}$ receptors will result in increased release of 5-HT *in vivo* and this should improve 5-HT neurotransmission. Accordingly, we believe that the compounds of this invention will be useful in the treatment of CNS disorders and that they will act as antidepressants *in vivo*.

In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were

specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

5-Nitro-1-chloroisoquinoline and 7-Nitro-1-chloroisoquinoline (D1)

A stirred solution of a mixture of 5- and 7-nitroisoquinolin-1-ols (*Chem. Pharm. Bull.* 1968, 16, 715; 3.8 g, 20 mmole) in $POCl_3$ (15 ml) under argon was heated under reflux for 3 h. After cooling the $POCl_3$ was removed *in vacuo* and the residue partitioned between DCM and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* giving the title compounds as a pale yellow solid (3.7 g, 89%). MS: m/z (MH^+) = 209.

Description 2

5-Nitro-1-(4-methylpiperazin-1-yl)isoquinoline and 7-Nitro-1-(4-methylpiperazin-1-yl)isoquinoline (D2)

A stirred solution of 1-chloro-5/7-nitroisoquinolines (D1, 1.8 g, 8.6 mmole) in DMF (20 ml) was treated with *N*-methyl piperazine (1.7 g, 17.2 mmole) and heated at 100° for 3 h. After cooling, the solvent was removed *in vacuo* and the residue partitioned between water and EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The residue was passed through a silica gel column eluting with DCM/MeOH/NH_4OH 19:1:0.1 giving the title compounds as a red oil (1.2 g, 51%). MS: m/z (MH^+) = 273.

Description 3

7-Amino-1-(4-methylpiperazin-1-yl)isoquinoline (D3)

A stirred solution of 1-(4-methylpiperazin-1-yl)-5/7-nitroisoquinolines (D2, 1.2 g, 4.4 mmole) in EtOH (50 ml) was treated with conc. HCl (5 ml) and $SnCl_2.2H_2O$ (4 g, 17.6 mmole) and heated under reflux for 15 h. The suspension was poured onto ice and basified with 40% NaOH. The aqueous suspension was extracted twice with EtOAc, and the combined organic layers washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography eluting with DCM/MeOH/NH_4OH 19:2:0.1 to give the title compound as a red-brown solid (140 mg, 13%).
MS: m/z (MH^+) = 243. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 7.96 (d, 1H), 7.59 (d, 1H), 7.22 (s, 1H), 7.14 (d, 1H), 7.07 (d, 1H), 3.98 (br. s, 2H), 3.38 (br. s, 4H), 2.69 (br. s, 4H), 2.40 (s, 3H).

Description 4

4-(4-Methyl-piperazin-1-yl)-6-nitro-quinazoline (D4)

A stirred solution of 4-chloro-6-nitroquinazoline (*J. Chem. Soc.* 1948, 360; 1.0 g, 4.8 mmole) in dry DCM under Ar was treated with *N*-methylpiperazine (1.06 ml, 9.6 mmole). After 18 h the solution was evaporated to dryness *in vacuo* and the residue partitioned between DCM and water. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo* to give the title compound as an orange gum (1.18 g, 90%).

MS: m/z (MH^+) = 274. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.83 (d, 1H), 8.75 (s, 1H), 8.46 (dd, 1H), 7.94 (d, 1H), 4.00 (t, 4H), 2.65 (t, 4H), 2.41 (s, 3H).

Description 5

6-Amino-4-(4-methyl-piperazin-1-yl)quinazoline (D5)

A stirred suspension of 4-(4-methylpiperazin-1-yl)-6-nitro-quinazoline (D4, 1.2 g, 4.3 mmole) and 10% Pd/C (150 mg) in EtOH was hydrogenated at 1 bar for 48 h, then filtered through kieselguhr. The filtrate and washings were concentrated to dryness to give the title compound as a yellow solid (1.01 g, 97%).

MS: m/z (MH^+) = 244. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.41 (s, 1H), 7.57 (d, 1H), 7.21 (d, 1H), 6.93 (s, 1H), 3.71 (br. s, 2H), 3.56 (br. s, 4H), 2.71 (br. s, 4H), 2.39 (s, 3H).

Description 6

Benzyl (1-benzyl)indole-6-carboxylate (D6)

A stirred solution of indole-6-carboxylic acid (5.4 g, 33 mmole) in DMF (100 ml) under argon was treated portionwise with sodium hydride (60% oil dispersion, 4.0 g, 100 mmole). After 30 minutes, benzyl bromide (16.5 ml, 140 mmole) was added and the solution stirred for 16 h at room temperature. After removal of the DMF *in vacuo* the residue was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc and the combined organics washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with DCM/hexanes (40:60) to afford a white crystalline solid (13.2 g, 90%).

MS: m/z (MH^+) = 342. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.12 (s, 1H), 7.84 (dd, 1H), 7.66 (d, 1H), 7.40 (m, 10H), 7.12 (dd, 1H), 6.58 (d, 1H), 5.36 (s, 4H).

Description 7

Benzyl (1-benzyl)indoline-6-carboxylate (D7)

A stirred solution of benzyl (1-benzyl)indole-6-carboxylate (D6, 6.8 g, 20 mmole) in acetic acid (35 ml) was treated with sodium cyanoborohydride (3.8 g, 60 mmole) in two portions. After 16 h, the acetic acid was removed *in vacuo* and the residue diluted with water, then basified with 2 M aqueous NaOH solution. Extraction with EtOAc followed

by washing with brine, drying over Na_2SO_4 and concentration *in vacuo* afforded a pale yellow solid (6.9 g, quant.).
MS: m/z (MH^+) = 344. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 7.30 (m, 11H), 7.18 (d, 1H), 7.11 (s, 1H), 5.32 (s, 2H), 4.29 (s, 2H), 3.35 (t, 2H), 3.00 (t, 2H).

Description 8

1-Benzylindoline-6-carboxylic acid (D8)

A solution of benzyl (1-benzyl)indoline-6-carboxylate (D7, 7.55 g, 22 mmole) in 1,4-dioxane (200 ml) was treated with 1 M aq. NaOH (200 ml), and heated under reflux for 16 h. Volatiles were removed *in vacuo* and the residue diluted with water, then acidified with 5 M aqueous HCl. Extraction with EtOAc, followed by washing with brine, drying over Na_2SO_4 and concentration *in vacuo* afforded a yellow solid (5.4 g, 85%).
MS: m/z (MH^+) = 342. 1H-NMR (250 MHz, d_6-DMSO) δ (ppm): 12.58 (s, 1H), 7.39-7.28 (m, 5H), 7.24 (dd, 1H), 7.11 (d, 1H), 7.02 (d, 1H), 4.31 (s, 2H), 3.35 (t, 2H), 2.96 (t, 2H).

Description 9

1-Benzylindoline-6-carboxylic acid (2,2-dimethoxyethyl)amide (D9)

A stirred solution of 1-benzylindoline-6-carboxylic acid (D8, 5.4 g, 19 mmole) in DMF (300 ml) was treated with triethylamine (3.5 ml, 25 mmole), EDC (4.6 g, 24 mmole), $HOBt.H_2O$ (3.7 g, 24 mmole) and aminoacetaldehyde dimethyl acetal (3.2 ml, 30 mmole). After 16h, the DMF was removed *in vacuo* and the residue diluted with water. Extraction with EtOAc, followed by washing with aqueous $NaHCO_3$, then brine, drying over Na_2SO_4 and concentration *in vacuo* afforded a buff waxy solid (6.3 g, 99%).
MS: m/z (MH^+) = 341. 1H-NMR (250 MHz, $CDCl_3$) δ (ppm): 7.26 (m, 5H), 7.08 (d, 1H), 7.01 (d, 1H), 6.95 (d, 1H), 6.24 (t, 1H), 4.47 (t, 1H), 4.30 (s, 2H), 3.57 (t, 2H), 3.43 (s, 6H), 3.36 (t, 2H), 2.99 (t, 2H).

Description 10

1-Benzyl-2,3-dihydro-8-hydroxypyrrolo[3,2-*g*]isoquinoline (D10)

A solution of 1-benzylindoline-6-carboxylic acid (2,2-dimethoxyethyl)amide (D9, 2.4 g, 7 mmole) in anhydrous THF (100 ml) was treated with $BF_3.Et_2O$ and the reaction mixture heated at 80°C for 16h under argon. The DMF was removed *in vacuo* and the residue partitioned between brine and EtOAc. Extraction of the aqueous with EtOAc, followed by washing of the combined organic phases with aqueous $NaHCO_3$, then brine, drying over Na_2SO_4 and concentration *in vacuo* afforded a brown solid (1.83 g, 94%).
MS: m/z (MH^+) = 277. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 10.80 (s, 1H), 7.33 (m, 7H), 6.95 (d, 1H), 6.45 (d, 1H), 4.43 (s, 2H), 3.42 (t, 2H), 3.10 (t, 2H).

Description 11

1-Benzyl-2,3-dihydro-8-trifluoromethanesulfonyloxy-pyrrolo[3,2-*g*]isoquinoline (D11)

An ice-cooled solution of 1-benzyl-2,3-dihydro-8-hydroxypyrrolo[3,2-*g*]isoquinoline (D10, 0.83 g, 3 mmole) in anhydrous DCM (10 ml) and pyridine (10 ml) was treated dropwise with trifluoromethanesulfonic anhydride (0.56 ml, 3.3 mmole). The reaction mixture was stirred under Ar at 0°C for 5 minutes, then at room temperature for 16h. After removal of the volatiles *in vacuo*, the residue was filtered through a short pad of silica eluting with DCM, giving a pale green solid (1.04g, 85%).

1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.87 (d, 1H), 7.37 (m, 7H), 6.68 (s, 1H), 4.46 (s, 2H), 3.60 (t, 2H), 3.20 (t, 2H).

Description 12

1-Benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D12)

A stirred solution of 1-benzyl-2,3-dihydro-8-trifluoromethanesulfonyloxy-pyrrolo[3,2-*g*]isoquinoline (D11, 680 mg, 1.67 mmole) in *N*-methylpiperazine (20 ml) was heated at 70° for 3 h, then concentrated to dryness *in vacuo*. Filtration through silica eluting with DCM/MeOH 19:1 gave the product as a brown solid (560 mg, 94%).

MS: m/z (MH^+): 359. 1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.91 (d, 1H), 7.33 (m, 6H), 7.08 (d, 1H), 6.70 (s, 1H), 4.41 (s, 2H), 3.55 (t, 2H), 3.27 (br. s, 4H), 3.16 (t, 2H), 2.55 (br. s, 4H), 2.37 (s, 3H).

Description 13

2,3-Dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13)

A stirred solution of 1-benzyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D12, 250 mg, 0.7 mmole) in EtOH (50 ml) under argon was treated with ammonium formate (1.5 g, 2.4 mmole) and 10% Pd/C (150 mg) and the reaction mixture refluxed for 20h under Ar atmosphere. The catalyst was removed by filtration through Kieselguhr and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography affording a brown solid (50 mg, 27%).

MS: m/z (MH^+) = 269. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 7.93 (d, 1H), 7.44 (s, 1H), 7.11 (d, 1H), 7.05 (s, 1H), 3.70 (t, 2H), 3.38 (br. s, 4H), 3.18 (t, 2H), 2.72 (br. s, 4H), 2.42 (s, 3H).

Description 14

Ethyl (N,N-dimethylamino)methylene acetoacetate (D14)

A solution of ethyl acetoacetate (2.6g, 20 mmole) and N,N-dimethylformamide dimethylacetal (6.6 ml, 50 mmole) was refluxed for 1.5h. After concentration *in vacuo*, the residue was diluted with brine, extracted with EtOAc. The combined organic phases

were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* affording an orange oil (3.4g, 91%).
1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 7.67 (s, 1H), 4.22 (q, 2H), 2.95 (br. s, 6H), 2.32 (s, 3H), 1.30 (t, 3H).

Description 15

Ethyl 1-(4-cyanophenyl)-5-methylpyrazole-4-carboxylate (D15)

A solution of ethyl (N,N-dimethylamino)methylene acetoacetate (D14, 0.37g, 2.0 mmole), 4-cyanophenyl hydrazine hydrochloride (0.34 g, 2.0 mmole) and triethylamine (0.31 ml, 2.2 mmole) in EtOH (10 ml) was stirred at room temperature for 2h. The ethanol was removed *in vacuo* and the residue partitioned between H_2O and Et_2O. The aqueous phase was extracted with ether and the combined organic phases washed with 1M aqueous HCl, followed by brine, then dried over Na_2SO_4 and concentrated *in vacuo*, affording a yellow solid (0.45 g, 88%).
MS: m/z (MH^+) = 256. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.06 (s, 1H), 7.80 (d, 2H), 7.61 (d, 2H), 4.35 (q, 2H), 2.64 (s, 3H), 1.41 (t, 3H).

Description 16

Ethyl 1-(4-cyanophenyl)-5-ethylpyrazole-4-carboxylate (D16)

The title compound was prepared from ethyl (N,N-dimethylamino)methylene propionoacetate (prepared from ethyl propionoacetate as per D14, 1.17 g, 5.9 mmole) and 4-cyanophenyl hydrazine hydrochloride (1.0 g, 5.9 mmole) according to the procedure for Description 15: pale brown crystals (1.4 g, 88%).
MS: m/z (MH^+) = 270. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.06 (s, 1H), 7.83 (d, 2H), 7.59 (d, 2H), 4.34 (q, 2H), 3.02 (q, 2H), 1.39 (t, 3H), 1.23 (t, 3H).

Description 17

1-Benzyl-2,3-dihydro-8-(4-*tert*-butyloxycarbonylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D17)

A solution of 1-benzyl-2,3-dihydro-8-trifluoromethanesulfonyloxy-pyrrolo[3,2-g]isoquinoline (D11, 408 mg, 1.0 mmole) and N-*tert*-butyloxycarbonyl piperazine (3.7g, 20 mmole) in DMF (4ml) was heated at 70°C for 5h. After concentration *in vacuo*, the residue was purified by flash chromatography on a silica column eluting with pentane/EtOAc (100:0 to 80:20) to afford an orange solid (270 mg, 61%).
MS: m/z (MH^+): 445. 1H-NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 7.91 (d, 1H), 7.36 (m, 6H), 7.11 (d, 1H), 6.66 (s, 1H), 4.42 (s, 2H), 3.59 (t, 2H), 3.48 (m, 4H), 3.16 (m, 6H), 1.48 (s, 9H).

Description 18

1-Benzyl-2,3-dihydro-8-(piperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D18)

A solution of 1-benzyl-2,3-dihydro-8-(4-*tert*-butyloxycarbonylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D17, 260 mg, 0.58 mmole) in TFA (1 ml) was stirred at room temperature for 1h. The TFA was removed *in vacuo* and the residue dissolved in DCM, and washed with an aqueous saturated solution of K_2CO_3. The organic phase was dried over Na_2SO_4, then concentrated *in vacuo* affording an orange solid (160 mg, 80%).

MS: m/z (MH^+): 345. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 7.92 (d, 1H), 7.33 (m, 6H), 7.09 (d, 1H), 6.70 (s, 1H), 4.42 (s, 2H), 3.58 (t, 2H), 3.17 (m, 6H), 2.97 (m, 4H).

Description 19

1-Benzyl-2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D19)

A solution of 1-benzyl-2,3-dihydro-8-(piperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D18, 0.64 g, 1.85 mmole) in THF (10 ml) was treated with 2-trifluoroacetoxypyridine (0.39 g, 2.05 mmole) and the reaction mixture stirred at room temperature for 1.5h. The THF was removed *in vacuo*, and the residue diluted with DCM, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography using EtOAc/pentane (15:85) afforded a yellow solid (0.51g, 63%).

MS: m/z (MH^+) = 441. 1H-NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 7.91 (d, 1H), 7.38 (m, 6H), 7.15 (d, 1H), 6.53 (s, 1H), 4.43 (s, 2H), 3.65 (m, 6H), 3.21 (m, 4H).

Description 20

1-Formyl-2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D20)

A solution of 1-benzyl-2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D19, 0.51g, 1.15 mmole) and 10% Pd/C (0.5g) in formic acid (60 ml) was stirred at 80°C for 1.5h. After cooling, the reaction mixture was filtered through Kieselguhr and concentrated *in vacuo*. Flash chromatography using EtOAc/Pentane (90:10) afforded a pale yellow solid (220mg, 51%).

MS: m/z (MH^+) = 379. 1H NMR (250 MHz, $CDCl_3$, free base, two rotamers): δ (ppm): 9.14 (s, 0.5H), 8.70 (s, 0.5H), 8.65 (s, 0.5H), 8.10 (m, 1H), 7.72 (s, 0.5H), 7.65 (s, 0.5H), 7.60 (s, 0.5H), 7.23 (m, 1H), 4.25 (t, 1H), 4.17 (t, 1H), 3.94 (m, 4H), 3.46 (m, 4H).

Description 21

2,3-Dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D21)

A solution of 1-formyl-2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D20, 210 mg, 0.55 mmole) in 2 M aqueous HCl (10 ml) was stirred at 70°C for 20 minutes. After cooling to 0°C, the reaction mixture was neutralized with

solid K_2CO_3, then extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, then concentrated *in vacuo* affording a pale brown solid (190 mg, 98%).
MS: m/z (MH^+) = 351. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 7.93 (d, 1H), 7.47 (s, 1H), 7.18 (d, 1H), 7.01 (s, 1H), 3.92 (br. t, 2H), 3.85 (br. t, 2H), 3.69 (t, 2H), 3.38 (m, 4H), 3.20 (t, 2H).

Description 22

Ethyl 4-ethyl-2-methyloxazole-5-carboxylate (D22)

A stirred solution of ethyl 2-chloropropionylacetate (12.4 g, 69 mmole) in glacial AcOH (24 ml) was treated with acetamide (8.2 g, 139 mmole) and heated at reflux, under argon, for 18h. On cooling, the mixture was concentrated *in vacuo*, diluted with H_2O (50 ml) and extracted with Et_2O (2 x 150 ml). The combined organic extracts were washed with dilute aqueous K_2CO_3 solution, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography, eluting with Et_2O/petrol gradient, to afford the title compound as a yellow oil (3.64 g, 29%).
MS: m/z (MH^+) = 184. ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 4.36 (q, 2H), 2.85 (q, 2H), 2.50 (s, 3H), 1.39 (t, 3H), 1.24 (t, 3H).

Description 23

***tert*-Butyl 1,2,3,6-tetrahydro-4-trimethylstannyl-pyridine-1-carboxylate (D23)**

A suspension of *tert*-butyl 1,2,3,6-tetrahydro-4-[(trifluoromethyl)sulfonyloxy]-pyridine-1-carboxylate (*Synthesis* 1991, 993; 500 mg, 1.51 mmole), hexamethylditin (550 mg, 1.68 mmole) and LiCl (374 mg, 9.01 mmole) in THF (20 ml) was degassed with Ar, treated with $Pd(PPh_3)_4$ (175 mg, 0.15 mmole) and heated under reflux for 16 h. After cooling the solution was diluted with petrol and washed with saturated aqueous $NaHCO_3$, dried (Na_2CO_3) and concentrated to dryness. The residue was filtered through silica (EtOAc/petrol 1:9) to give a colourless oil (506 mg, 97%).
^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 5.77 (br. s, 1H), 3.91 (m, 2H), 3.47 (t, 2H), 2.28 (br. s, 2H), 1.47 (s, 9H), 0.12 (s, 9H).

Description 24

1-Benzyl-2,3-dihydro-8-(1-*tert*-butyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)pyrrolo[3,2-g]isoquinoline (D24)

A solution of 1-benzyl-2,3-dihydro-8-trifluoromethanesulfonyloxy-pyrrolo[3,2-g]isoquinoline (D11, 1.90 g, 4.66 mmole) and *tert*-butyl 1,2,3,6-tetrahydro-4-trimethylstannylpyridine-1-carboxylate (D23, 2.13 g, 6.16 mmole) in DMF (20ml) was degassed with Ar for 20 min, treated with CuI (27 mg, 0.14 mmole) and $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmole), and heated at 110° for 16 h. The mixture was concentrated to dryness *in vacuo* and partitioned between saturated $NaHCO_3$ and DCM. The organic

layer was dried (Na_2SO_4) and concentrated to dryness. Filtration of the residue (silica, EtOAc/petrol 1:19) gave the product as a yellow oil (853 mg, 42%).
MS: m/z (MH^+) = 442. ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.19 (d, 1H), 7.43 (s, 1H), 7.37-7.26 (m, 6H), 6.70 (br. s, 1H), 5.80 (br. s, 1H), 4.39 (s, 2H), 4.04 (br. s, 2H), 3.63 (t, 2H), 3.57 (t, 2H), 3.18 (t, 2H), 2.54 (br. s, 2H), 1.51 (s, 9H).

Description 25

1-Benzyl-2,3-dihydro-8-(1-*tert*-butyloxycarbonylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D25)

A solution of 1-benzyl-2,3-dihydro-8-(1-*tert*-butyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)pyrrolo[3,2-g]isoquinoline (D24, 850 mg, 1.93 mmole) in MeOH (30 ml) was hydrogenated over Pd/C (10%, 1.2 g) for 18 h. After filtration through Kieselguhr the solvent was removed *in vacuo* giving a colourless glass (842 mg, 99%).
MS: m/z (MH^+) = 444.

Description 26

1-Benzyl-2,3-dihydro-8-(piperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D26)

A solution of 1-benzyl-2,3-dihydro-8-(1-*tert*-butyloxycarbonylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D25, 840 mg, 1.90 mmole) in trifluoroacetic acid (10 ml) was stirred at room temperature for 15 h, then concentrated to dryness *in vacuo*. The residue was partitioned between saturated aqueous K_2CO_3 and DCM, and the aqueous layer extracted twice with DCM. Combined organic layers were dried (Na_2SO_4) and concentrated to dryness giving a yellow oil (350 mg, 54%). MS: m/z (MH^+) = 344.

Description 27

1-Benzyl-2,3-dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D27)

A solution of 1-benzyl-2,3-dihydro-8-(piperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D26, 350 mg, 1.02 mmole) in methanol (10 ml) was treated with formaldehyde (37% aqueous, 0.60 ml) and $NaBH_4CN$ (200 mg, 2.86 mmole), and stirred at room temperature for 2 h. The solution was concentrated *in vacuo* and the residue partitioned between DCM and 1 M NaOH solution. The aqueous layer was extracted with DCM and the combined organic layers dried (Na_2SO_4) and concentrated to dryness *in vacuo*, giving a yellow oil (190 mg, 52%). MS: m/z (MH^+) = 358.

Description 28

1-Formyl-2,3-dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D28)

The title compound was prepared from 1-benzyl-2,3-dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D27, 190 mg, 0.53 mmole) according to the procedure in Description D20: pale brown crystals (80 mg, 63%). MS: m/z (MH^+) = 296.

Description 29

2,3-Dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D29)

The title compound was prepared from 1-formyl-2,3-dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D28, 80 mg, 0.27 mmole) according to the procedure in Description D21: buff crystals (68 mg, 94%).

MS: m/z (MH^+) = 268. ^1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.22 (d, 1H), 7.49 (s, 1H), 7.33 (d, 1H), 6.96 (s, 1H), 4.27 (br. s, 1H), 3.69 (t, 2H), 3.48 (m, 2H), 3.21 (t, 2H), 2.83 (s, 3H), 2.80 (m, 2H), 2.66 (m, 2H), 1.93 (br. d, 2H).

Description 30

Ethyl 1-(3-cyanophenyl)-5-trifluoromethylpyrazole-4-carboxylate (D30)

A solution of ethyl ethoxymethylene-3-oxo-4,4,4-trifluorobutyrate (1.7 g, 6 mmol) in EtOH (4ml) was added over a 1.5h period to a solution of 3-cyanophenylhydrazine (1.0 g, 6 mmol) and triethylamine (0.8 ml, 6.6 mmol) in EtOH (20 ml) at 0°C. The reaction was allowed to warm up to room temperature and stirred for 20h. After removal of the EtOH *in vacuo*, the residue was purified by silica chromatography affording a yellow solid (180 mg, 10%).

1H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.15 (s, 1H), 7.78 (dd, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.63 (d, 1H), 4.38 (q, 2H), 1.39 (t, 3H).

Description 31

Ethyl 1-(4-cyanophenyl)-3-trifluoromethylpyrazole-4-carboxylate (D31)

A solution of ethyl 3-trifluoromethylpyrazole-4-carboxylate (8.5 g, 41 mmol) in DMF (200 ml) was treated portionwise with sodium hydride (60% oil dispersion, 1.95 g, 48 mmol) and the reaction mixture stirred at room temperature under Ar for 1h. 4-fluorobenzonitrile (5.3 g, 44 mmol) was added and the mixture stirred at 110°C for 16h. After cooling to room temperature, the reaction was quenched with water, then concentrated *in vacuo*. The residue was purified by silica chromatography affording a white solid (11.1g, 88%).

1H NMR (400 MHz, $CDCl_3$): δ (ppm): 8.56 (s, 1H), 7.90 (d, 2H), 7.84 (d, 2H), 4.37 (q, 2H), 1.39 (t, 3H).

Description 32

3-Aminosalicylic acid ethyl ester (D32)

A solution of 3-amino salicylic acid (0.75g, 4.9 mmol) in EtOH (30 ml) and concentrated H_2SO_4 (5 ml) was stirred at room temperature for 3h. After concentration *in vacuo*, the residue was diluted with water, treated with solid K_2CO_3 and extracted with EtOAc.

After drying over Na_2SO_4, concentration of the organic phase *in vacuo* afforded a brown oil 0.41g (46%).
MS: m/z (MH^+) =182. 1H-NMR (400 MHz, $CDCl_3$): δ (ppm): 7.25 (d, 1H), 6.88 (d, 1H), 6.71 (t, 1H), 4.37 (q, 2H), 1.41 (t, 3H).

Description 33

4*H*-3-Oxo-benz[1,4]oxazine-8-carboxylic acid ethyl ester (D33)

A solution of 3-aminosalicylic acid ethyl ester (D32) (0.41 g, 2.1 mmol) in DMF (20 ml) was treated with chloroacetyl chloride (0.185 ml, 2.3 mmol) and stirred at room temperature for 20 minutes. Solid K_2CO_3 (1.38 g, 10 mmol) was then added portionwise and the reaction stirred at room temperature for 16 h under Ar. After concentration *in vacuo*, the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, then concentrated *in vacuo*, affording a brown solid (0.41g, 88%).
MS: m/z (MH^+) = 220. 1H-NMR (250 MHz, $CDCl_3$): δ (ppm): 8.72 (s, 1H), 7.52 (dd, 1H), 7.02 (d, 1H), 6.99 (s, 1H), 4.72 (s, 2H), 4.36 (q, 2H), 1.36 (t, 3H).

Description 34

Ethyl 1-(4-methoxyphenyl)-5-methylpyrazole-4-carboxylate (D34)

The title compound was prepared from ethyl (N,N-dimethylamino)methylene acetoacetate (D14, 1.02 g, 5.1 mmole) and 4-methoxyphenyl hydrazine hydrochloride (0.89 g, 5.1 mmole) according to the procedure for Description 15: pale brown crystals (0.99 g, 84%).
MS: m/z (MH^+) = 233.

Description 35

Ethyl 1-(4-methoxyphenyl)-5-ethylpyrazole-4-carboxylate (D35)

The title compound was prepared from ethyl (N,N-dimethylamino)methylene propionoacetate (prepared from ethyl propionoacetate as per D14, 1.08 g, 5.4 mmole) and 4-methoxyphenyl hydrazine hydrochloride (0.92 g, 5.4 mmole) according to the procedure for Description 15: buff solid (1.21 g, 91%). MS: m/z (MH^+) = 289.

Description 36

Ethyl 1-(4-methoxyphenyl)-5-isopropylpyrazole-4-carboxylate (D36)

The title compound was prepared from ethyl (N,N-dimethylamino)methylene propionoacetate (prepared from ethyl isobutyrylacetate as per D14, 1.28 g, 6.2 mmole) and 4-methoxyphenyl hydrazine hydrochloride (1.08 g, 6.2 mmole) according to the procedure for Description 15: pale yellow solid (1.31 g, 81%). MS: m/z (MH^+) = 261.

Description 37

Ethyl 1-(4-cyanophenyl)-5-isopropylpyrazole-4-carboxylate (D37)

The title compound was prepared from ethyl (*N,N*-dimethylamino)methylene isobutyrylacetate (prepared from ethyl isobutyrylacetate as per D14, 1.70 g, 8.0 mmole) and 4-cyanophenyl hydrazine hydrochloride (1.36 g, 8.0 mmole) according to the procedure for Description 15: orange solid (2.1 g, 93%). MS: m/z (MH^+) = 284.

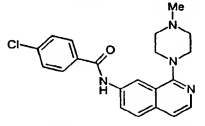
Description 38

Ethyl 4-methyl-2-(4-cyanophenyl)oxazole-5-carboxylate (D38)

A stirred solution of ethyl 2-chloroacetoacetate (5.0 g, 30 mmole) in glacial AcOH (10 ml) was treated with 4-cyanobenzamide (*J. Med. Chem.* 1991, 34, 1630; 8.9 g, 61 mmole) and heated at reflux, under argon, for 20h. On cooling, the mixture was concentrated *in vacuo*, diluted with H_2O (50 ml) and extracted with Et_2O (2 x 150 ml). The combined organic extracts were washed with dilute aqueous K_2CO_3 solution, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography, eluting with Et_2O/petrol gradient, to afford the title compound as a yellow oil (0.26 g, 3%). MS: m/z (MH^+) = 257.

Example 1

7-(4-Chlorobenzamido)-1-(4-methylpiperazin-1-yl)isoquinoline (E1)

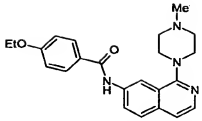


A stirred solution of 7-amino-1-(4-methylpiperazin-1-yl)isoquinoline (D3, 110 mg, 0.45 mmole) in DCM (5 ml) was treated with Et_3N (91 mg, 0.90 mmole), DMAP (cat.) and 4-chlorobenzoyl chloride (95 mg, 0.54 mmole). After 48 h the solution was diluted with DCM, washed with water, dried over $MgSO_4$, filtered and concentrated to dryness *in vacuo*. The residue was purified by flash chromatography giving the title compound as a pale brown solid (80 mg, 46%).

MS: m/z (MH^+) = 381/383. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.59 (s, 1H), 8.15-8.05 (m, 2H), 7.90-7.80 (m, 2H), 7.80-7.60 (m, 2H), 7.55-7.45 (m, 2H), 7.23 (br. s, 1H), 3.49 (br. s, 4H), 2.78 (br. s, 4H), 2.43 (s, 3H).

Example 2

7-(4-Ethoxybenzamido)-1-(4-methylpiperazin-1-yl)isoquinoline (E2)

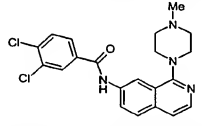


A stirred solution of 4-ethoxybenzoic acid (32 mg, 0.21 mmole), HOBt (29 mg, 0.21 mmole) and 7-amino-1-(4-methylpiperazin-1-yl)isoquinoline (D3, 35 mg, 0.14 mmole) in DMF (2 ml) was treated with polystyrylmethyl cyclohexyl carbodiimide (200 mg resin, 0.28 mmole) and heated at 60° for 72 h. After filtration the solution was concentrated to dryness and purified by preparative thin layer chromatography eluting with DCM/MeOH/NH_4OH 19:1:0.1 to give the title compound as an off white solid (30 mg, 53%).

MS: m/z (MH^+) = 391. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.57 (s, 1H), 8.10 (d, 1H), 8.08 (s, 1H), 7.88 (d, 2H), 7.71 (s, 2H), 7.20 (d, 1H), 6.95 (d, 2H), 4.09 (q, 2H), 3.50 (br. s, 4H), 2.79 (br. s, 4H), 2.43 (s, 3H), 1.45 (t, 3H).

Example 3

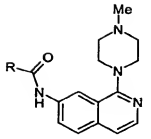
7-(3,4-Dichlorobenzamido)-1-(4-methylpiperazin-1-yl)isoquinoline (E3)

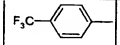
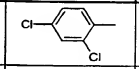
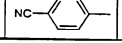
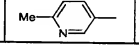


The title compound was prepared from 3,4-dichlorobenzoic acid and 7-amino-1-(4-methylpiperazin-1-yl)isoquinoline (D3, 35 mg, 0.14 mmole) according to the procedure for Example 2, giving a red-brown solid (46 mg, 79%).

MS: m/z (MH^+) = 415. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.57 (s, 1H), 8.36 (br. s, 1H), 8.11 (d, 1H), 8.01 (d, 1H), 7.75-7.65 (m, 3H), 7.54 (d, 1H), 7.20 (d, 1H), 3.46 (br. s, 4H), 2.71 (br. s, 4H), 2.37 (s, 3H).

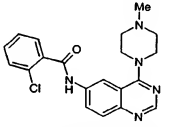
Examples E4 - E7 were prepared using a similar procedure to that used for Example 2.



Example	R	MH+	Example	R	MH+
E4		415	E5		415
E6		372	E7		362

Example 8

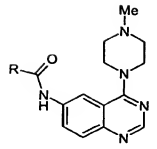
6-(2-Chlorobenzamido)-4-(4-methylpiperazin-1-yl)quinazoline (E8)

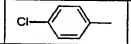
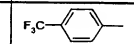
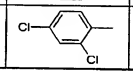
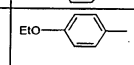


The title compound was prepared from 2-chlorobenzoic acid and 6-amino-4-(4-methylpiperazin-1-yl)quinazoline (D5, 97 mg, 0.39 mmole) according to the procedure for Example 2, giving a brown glass (115 mg, 74%).

MS: m/z (MH^+) = 382. 1H NMR (250 MHz, $CDCl_3$): δ (ppm): 8.78 (s, 1H), 8.67 (s, 1H), 8.52 (br. s, 1H), 7.85 (d, 1H), 7.75 (dd, 1H), 7.56 (dd, 1H), 7.43 (m, 3H), 3.87 (br. s, 4H), 2.69 (br. s, 4H), 2.39 (s, 3H).

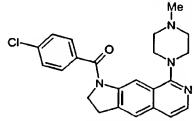
Examples E9 – E12 were prepared using a similar procedure to that described for Example 8.



Example	R	MH+	Example	R	MH+
E9		382	E11		416
E10		416	E12		392

Example 13

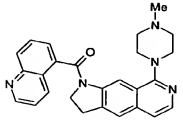
1-(4-Chlorobenzoyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E13)



A stirred solution of 4-chlorobenzoic acid (44 mg, 0.28 mmole), *N,N*-diisopropyl carbodiimide(0.045 ml, 0.28 mmole) and HOBt.H_2O (43 mg, 0.28 mmole) in DMF (3 ml) was treated with a solution of 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D13, 50 mg, 0.18 mmole) and Et_3N (0.1 ml) in DMF (5 ml) and heated at 60°C for 16h under argon. After cooling, the solution was transferred to an SCX column, washing with MeOH followed by DCM. The product was eluted with 1M methanolic ammonia. Concentration *in vacuo* afforded a pale beige solid which was transformed into the HCl salt by treatment with 1 M HCl in Et_2O: yellow solid (62 mg, 78%).
MS: m/z (MH^+) = 407. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.90 (br. s, 1H), 8.07 (d, 1H), 7.61 (s, 1H), 7.57 (s, 2H), 7.48 (s, 1H), 7.45 (s, 1H), 7.15 (d, 1H), 4.18 (br. s, 2H), 3.38 (br. s, 4H), 3.28 (t, 2H), 2.70 (br. s, 4H), 2.38 (s, 3H).

Example 14

1-(Quinolin-5-carbonyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E14)

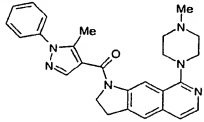


A stirred solution of 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 75 mg, 0.28 mmole) and ethyl quinoline-5-carboxylate (84 mg, 0.42 mmole) in dry toluene (5 ml) was treated with $AlMe_3$ (2M in toluene, 0.56 ml) and heated under reflux for 18 h. The solution was passed directly through a silica column eluting with DCM/MeOH 9:1 to give the product which was converted to the hydrochloride using 1M HCl in Et_2O: yellow solid (78 mg, 66%).

MS: m/z (MH^+) = 424. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 9.10 (br. s, 1H), 8.99 (dd, 1H), 8.23 (br. d, 1H), 8.24 (br. d, 1H), 8.11 (m, 1H), 7.80 (t, 1H), 7.68 (d, 1H), 7.58 (s, 1H), 7.47 (dd, 1H), 7.15 (m, 1H), 3.87 (br. s, 2H), 3.66 (br. s, 4H), 3.31 (m, 2H), 2.80 (br. s, 4H), 2.40 (s, 3H).

Example 15

2,3-Dihydro-1-(5-methyl-1-phenylpyrazol-4-yl carbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E15)

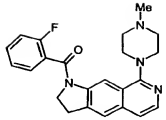


The title compound was prepared from 5-methyl-1-phenylpyrazole-4-carboxylic acid (170 mg, 0.84 mmole) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 150 mg, 0.56 mmole) using a similar procedure to Example 13. The compound was converted to its hydrochloride salt: yellow solid (176 mg, 68%).

MS: m/z (MH^+) = 453. ^1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.62 (br. s, 1H), 8.07 (d, 1H), 7.88 (s, 1H), 7.58 (s, 1H), 7.53-7.46 (m, 5H), 7.16 (d, 1H), 4.38 (t, 2H), 3.45 (br. s, 4H), 3.34 (t, 2H), 2.72 (br. s, 4H), 2.56 (s, 3H), 2.38 (s, 3H).

Example 16

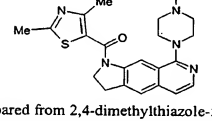
1-(2-Fluorobenzoyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E16)



The title compound was prepared from 2-fluorobenzoic acid (157 mg, 1.12 mmole) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 150 mg, 0.56 mmole) using a similar procedure to Example 13. The compound was converted to its hydrochloride salt: yellow solid (176 mg, 74%).
MS: m/z (MH^+) = 391. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.97 (s, 1H), 8.08 (d, 1H), 7.58-7.42 (m, 3H), 7.30-7.18 (m, 2H), 7.15 (d, 1H), 4.03 (t, 2H), 3.51 (br. s, 4H), 3.26 (t, 2H), 2.79 (br. s, 4H), 2.41 (s, 3H).

Example 17

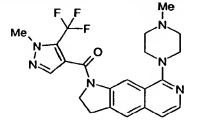
2,3-Dihydro-1-(2,4-dimethylthiazol-5-yl carbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E17)



The title compound was prepared from 2,4-dimethylthiazole-5-carboxylic acid (26 mg, 0.17 mmole) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 30 mg, 0.11 mmole) using a similar procedure to Example 13. The compound was converted to its hydrochloride salt: yellow solid (37 mg, 75%).
MS: m/z (MH^+) = 408. ^1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.38 (br. s, 1H), 8.08 (d, 1H), 7.57 (s, 1H), 7.14 (d, 1H), 4.19 (t, 2H), 3.39 (br. s, 4H), 3.31 (t, 2H), 2.74 (s, 3H), 2.67 (br. s, 4H), 2.50 (s, 3H), 2.40 (s, 3H).

Example 18

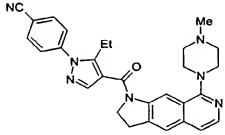
1-(1-methyl-5-trifluoromethylpyrazol-4-carbonyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E18)



A stirred solution of 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D13, 107 mg, 0.4 mmole) and ethyl 1-methyl-5-trifluoromethylpyrazole-4-carboxylate (107 mg, 0.48 mmole) in dry toluene (5 ml) under Ar was treated with 2M $AlMe_3$ in toluene (0.30 ml, 0.6 mmole) and the reaction mixture refluxed for 20h. After cooling, the mixture was transferred to a silica column, eluting with 10% MeOH in CH_2Cl_2. Concentration *in vacuo* afforded a pale beige solid which was transformed into the HCl salt by treatment with 1 M HCl in Et_2O: yellow solid (98 mg, 55%).
MS: m/z (MH) = 445^+. 1H-NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.85 (br. s, 1H), 8.08 (d, 1H), 7.67 (s, 1H), 7.56 (s, 1H), 7.14 (d, 1H), 4.09 (br. t, 2H), 4.03 (s, 3H), 3.32 (br. s, 4H), 3.29 (t, 2H), 2.70 (br. s, 4H), 2.41 (s, 3H).

Example 19

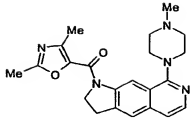
1-[1-(4-cyanophenyl)-5-ethylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E19)



The title compound was prepared from 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 1.00 g, 3.72 mmole) and ethyl 1-(4-cyanophenyl)-5-ethylpyrazole-4 carboxylate (D16, 1.00 g, 3.72 mmole) according to the procedure described in Example 18: yellow solid (1.36 g, 74%).
MS: m/z (MH) = 492^+. 1H-NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.58 (br. s, 1H), 8.09 (d, 1H), 7.88 (s, 1H), 7.86 (d, 2H), 7.66 (d, 2H), 7.59 (s, 1H), 7.19 (d, 1H), 7.16-7.14 (m, 2H), 4.33 (t, 2H), 3.42 (br. s, 4H), 3.34 (t, 2H), 3.06 (q, 3H), 2.66 (br. s, 4H), 2.36 (s, 3H).

Example 20

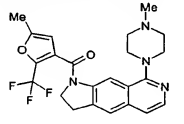
1-(2,4-dimethyloxazol-5-ylcarbonyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E20)



The title compound was prepared from 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 80 mg, 0.3 mmole) and ethyl 2,4-dimethyloxazole-5-carboxylate (*J. Heterocycl. Chem.* 1998, 35, 859; 85 mg, 0.6 mmole) according to the procedure described in Example 18: yellow solid (60 mg, 51%).
MS: m/z (MH) = 392^+. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.75 (br. s, 1H), 8.07 (d, 1H), 7.56 (s, 1H), 7.14 (d, 1H), 4.45 (t, 2H), 3.49 (br. s, 4H), 3.36 (t, 2H), 2.82 (br. s, 4H), 2.52 (s, 6H), 2.46 (s, 3H).

Example 21

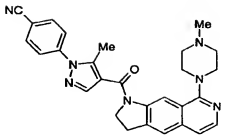
2,3-Dihydro-1-(5-methyl-2-trifluoromethylfuran-3-ylcarbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E21)



The title compound was prepared from 5-methyl-2-trifluoromethylfuran-3-carboxylic acid (54 mg, 0.28 mmole) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 50 mg, 0.19 mmole) using a similar procedure to Example 13. The compound was converted to its hydrochloride salt: pale yellow solid (67 mg, 76%).
MS: m/z (MH) = 445^+. ^{1}H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.91 (s, 1H), 8.08 (d, 1H), 7.55 (s, 1H), 7.14 (d, 1H), 6.24 (s, 1H), 4.02 (t, 2H), 3.49 (br. s, 4H), 3.30 (t, 2H), 2.79 (br. s, 4H), 2.42 (s, 6H).

Example 22

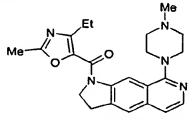
1-[1-(4-cyanophenyl)-5-methylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E22)



The title compound was prepared from 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D13, 40 mg, 0.15 mmole) and ethyl 1-(4-cyanophenyl)-5-methylpyrazole-4 carboxylate (D15, 61 mg, 0.24mmole) according to the procedure described in Example 18: yellow solid (31 mg, 42%).
MS: m/z (MH) = 478$^+$. 1H-NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.60 (br. s, 1H), 8.07 (d, 1H), 7.90 (s, 1H), 7.82 (d, 2H), 7.66 (d, 2H), 7.56 (s, 1H), 7.23 (d, 1H), 4.33 (t, 2H), 3.44 (br. s, 4H), 3.32 (t, 2H), 2.66 (br. s, 4H), 2.62 (s, 3H), 2.34 (s, 3H).

Example 23

2,3-Dihydro-1-(4-ethyl-2-methyloxazol-5-yl carbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E23)

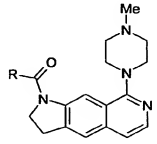


A solution of ethyl 4-ethyl-2-methyloxazole-5-carboxylate (D22 , 67 mg, 0.36 mmole) and 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D13, 75 mg, 0.28 mmole) in dry toluene (5 ml), was treated with a solution of $AlMe_3$ in toluene (2M, 0.2 ml) and stirred, under argon, at 110°C for 20h. The reaction mixture was then cooled and purified directly by flash silica chromatography, eluting with a MeOH/DCM gradient, to afford the title compound as a pale yellow solid. The compound was converted to its hydrochloride salt: yellow solid (52 mg, 42%).
MS: m/z (MH) = 406$^+$. ^{1}H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.71 (br.s, 1H), 8.07 (d, 1H), 7.56 (s, 1H), 7.14 (d, 1H), 4.43 (t, 2H), 3.47 (br. s, 4H), 3.35 (t, 2H), 2.94 (q, 2H), 2.76 (br. s, 4H), 2.53 (s, 3H), 2.45 (s, 3H), 1.31 (t, 3H).

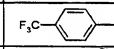
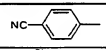
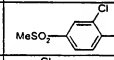
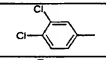
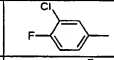
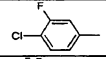
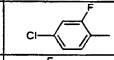
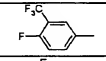
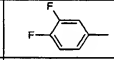
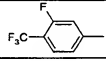
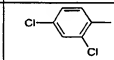
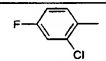
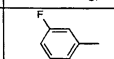
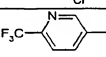
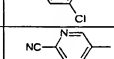
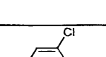
Examples E24 - E78

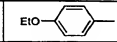
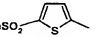
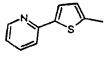
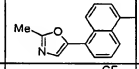
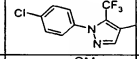
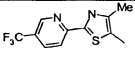
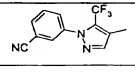
Examples E24 - E78 were prepared according to the procedure described for Examples 13 or 18 using acids or esters from commercial sources except: Examples 54 and 78 (WO 00/35919); Example 61 (*J. Amer. Chem. Soc.* 1992, 114, 8783); Example 65 (Description

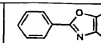
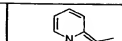
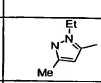
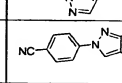
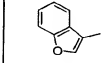
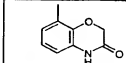
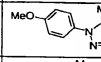
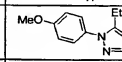
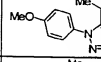
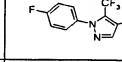
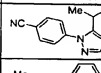
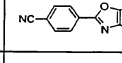
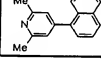
30); Example 67 (*Chem. Pharm. Bull.* 1974, 22, 1814); Example 69 (Description 31); Examples 71-74 (Descriptions 33-36); and Examples 76-77 (Descriptions 37-38).



5

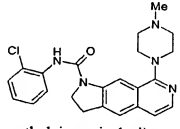
Example	R	MH+	Example	R	MH+
E24		441	E25		398
E26		485	E27		441
E28		425	E29		425
E30		425	E31		459
E32		409	E33		459
E34		441	E35		425
E36		425	E37		442
E38		399	E39		407

E40		409	**E41**		409
E42		417	**E43**		457
E44		388	**E45**		423
E46		424	**E47**		424
E48		424	**E49**		424
E50		424	**E51**		423
E52		456	**E53**		448
E54		504	**E55**		424
E56		541	**E57**		398
E58		403	**E59**		476
E60		456	**E61**		377
E62		422	**E63**		539
E64		409	**E65**		532

E66		508	**E67**		413
E68		405	**E69**		532
E70		413	**E71**		444
E72		483	**E73**		497
E74		511	**E75**		525
E76		505	**E77**		479
E78		528			

Example 79

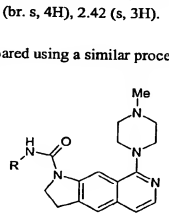
1-(2-Chlorophenyl)aminocarbonyl-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E79)

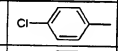
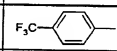
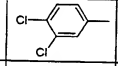
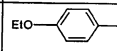
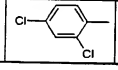


A solution of 2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (D13, 25 mg, 0.09 mmole) in DCM was treated with 2-chlorophenylisocyanate (16 mg, 0.11 mmole). After 24h the solution was loaded onto an SCX cartridge, washing with DCM and MeOH. The product was eluted with methanolic ammonia and concentrated to dryness, giving a yellow glass, which was converted to the hydrochloride salt by treatment with ethereal HCl (1M) and concentration to dryness: yellow powder (19 mg, 44%).

MS: m/z (MH^+) = 422/424. ^1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.57 (br.s, 1H), 8.39 (m, 1H), 8.05 (d, 1H), 7.53 (s, 1H), 7.38 (m, 2H), 7.07 (d, 1H), 7.04 (m, 2H), 4.24 (t, 2H), 3.42 (m, 6H), 2.74 (br. s, 4H), 2.42 (s, 3H).

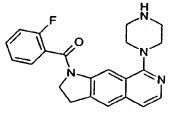
Examples E80 - E84 were prepared using a similar procedure to that described for Example 79.



Example	R	MH^+	Example	R	MH^+
E80		422	E81		456
E82		456	E83		432
E84		456			

Example 85

1-(2-Fluorobenzoyl)-2,3-dihydro-8-(piperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E85)



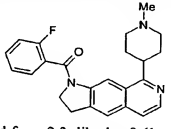
A stirred solution of 2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D21, 49 mg, 0.14 mmole), *N,N*-diisopropyl carbodiimide(0.036 ml, 0.35 mmole) and $HOBT.H_2O$ (54 mg, 0.35 mmole) in DMF (6 ml) was treated with 2-fluorobenzoic acid (39 mg, 0.28 mmole) and stirred at room temperature for 72h under argon. The reaction was quenched with N-methylamino polystyrene resin (240 mg, ~0.35 mmole) and stirred at room temperture for 16h. After filtration of the resin, the solution

was transferred to an SCX column, eluting with DCM followed by MeOH. The product was eluted with 1M methanolic ammonia. Concentration *in vacuo* afforded a pale brown solid which was stirred at room temperature for 16h in a solution of MeOH (5 ml) and 1M aqueous K_2CO_3 (0.8 ml). After concentration *in vacuo*, the residue was partitioned between H_2O and $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After purification by preparative TLC using DCM/MeOH (80:20), the product was obtained as a pale beige solid which was transformed into the HCl salt by treatment with 1 M HCl in Et_2O: yellow solid (11 mg, 19%).

MS: m/z (MH^+) = 377. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.93 (s, 1H), 8.09 (d, 1H), 7.58 (s, 1H), 7.51 (m, 2H), 7.28 (t, 1H), 7.16 (d, 2H), 4.05 (t, 2H), 3.57 (br. s, 4H), 3.30 (t, 2H), 3.22 (br. s, 4H), 2.94 (br. s, 1H).

Example 86

2,3-Dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (E86)

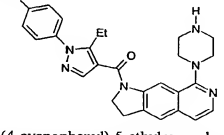


The title compound was prepared from 2,3-dihydro-8-(1-methylpiperidin-4-yl)pyrrolo[3,2-g]isoquinoline (D29, 68 mg, 0.25 mmole) and 2-fluorobenzoic acid according to the procedure in Example 13: yellow powder (61 mg, 56%).

MS: m/z (MH^+) = 390. 1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 9.11 (s, 1H), 8.41 (d, 1H), 7.62 (s, 1H), 7.57-7.45 (m, 2H), 7.40-7.28 (m, 2H), 7.20 (t, 1H), 4.07 (t, 2H), 3.60 (br. t, 1H), 3.31 (t, 2H), 3.09 (br. d, 2H), 2.38 (s, 3H), 2.37-1.92 (m, 6 H).

Example 87

1-[1-(4-Cyanophenyl)-5-ethylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(piperazin-1-yl)pyrrolo[3,2-g]isoquinoline (E87)

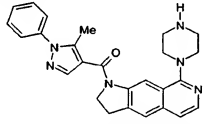


A stirred solution of ethyl 1-(4-cyanophenyl)-5-ethylpyrazole-4-carboxylate (D16, 86 mg, 0.25 mmole) and 2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-

g]isoquinoline (D21, 95 mg, 0.27 mmol) in dry toluene (10 ml) under Ar was treated with a solution of trimethylaluminium in toluene (2.0 M, 0.24 ml, 0.48 mmol) and heated at 100C for 65 h. After cooling the solution was transferred directly onto a silica gel column, which was eluted with MeOH/DCM (1:4). The filtrate was loaded onto an SCX column, washing with DCM followed by MeOH. The intermediate amide was eluted with methanolic ammonia (1.0 M) in a single fraction, which was concentrated to dryness giving a brown solid. A solution of this residue in MeOH (8 ml) was treated with aqueous K_2CO_3 solution (1.0 M, 2 ml), and stirred for 20 h, then concentrated under vacuum. The residue was diluted with water and extracted with $CHCl_3$ (4 x). Combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The title compound was obtained by preparative thin layer chromatography on silica gel, eluting with MeOH/DCM (1:4), and converted to the hydrochloride using a solution of HCl in Et_2O (1.0 M) - yellow solid (44 mg, 36%).
MS: m/z (MH^+) = 478. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.55 (br. s, 1H), 8.08 (d, 1H), 7.88-7.82 (m, 3H), 7.64 (m, 2H), 7.59 (s, 1H), 7.18 (d, 1H), 4.35 (t, 2H), 3.45 (br.s, 4H), 3.35 (t, 2H), 3.20 (br.s, 4H), 3.04 (q, 2H), 1.19 (t, 3H). NH not discernible.

Example 88

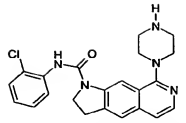
2,3-Dihydro-1-(5-methyl-1-phenylpyrazol-4-yl carbonyl)-8-(piperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline (E88)



The title compound was prepared from ethyl 5-methyl-1-phenylpyrazole-4-carboxylate (76 mg, 0.33 mmole) and 2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D21, 95 mg, 0.27 mmol) using a similar procedure to Example 83. The compound was converted to its hydrochloride salt: yellow solid (74 mg, 48%).
MS: m/z (MH^+) = 439. ^1H NMR (250 MHz, $CDCl_3$, free base): δ (ppm): 8.59 (br. s, 1H), 8.06 (d, 1H), 7.87 (s, 1H), 7.58-7.40 (m, 6H), 7.13 (d, 1H), 4.36 (t, 2H), 3.35 (br. s, 4H), 3.30 (t, 2H), 3.10 (br. s, 4H), 2.53 (s, 3H). NH not discernible.

Example 89

1-(2-Chlorophenyl-1-aminocarbonyl)-8-(piperazin-1-yl)-2,3-dihydropyrrolo[3,2-*g*]isoquinoline (E89)

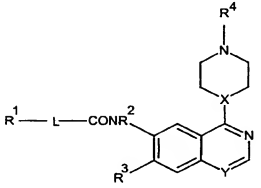


A stirred solution of 2,3-dihydro-8-(4-trifluoroacetylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline (D21, 84 mg, 0.24 mmole) in DCM (5 ml) was treated with 2-chlorophenylisocyanate (74 mg, 0.48 mmole). After 65 h the solution was loaded onto an SCX column, washing with DCM followed by MeOH. The intermediate urea was eluted with methanolic ammonia (1.0 M) in a single fraction, which was concentrated to dryness giving a brown solid. A solution of this residue in MeOH (8 ml) was treated with aqueous K_2CO_3 solution (1.0 M, 2 ml), and stirred for 20 h, then concentrated under vacuum. The residue was diluted with water and extracted with $CHCl_3$ (4 x). Combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The title compound was obtained by preparative thin layer chromatography on silica gel, eluting with MeOH/DCM (1:4), and converted to the hydrochloride using a solution of HCl in Et_2O (1.0 M) - yellow solid (40 mg, 38%).

MS: m/z (MH^+) = 408. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.58 (s, 1H), 8.38 (dd, 1H), 8.05 (d, 1H), 7.52 (s, 1H), 7.40-7.30 (m, 2H), 7.13 (d, 1H), 7.03 (dt, 1H), 4.23 (t, 2H), 3.43-3.36 (m, 6H), 3.19-3.16 (m, 4H). Piperazine NH and urea NH not discernible.

CLAIMS

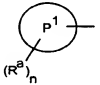
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which R^1 is selected from a group of formula (i) or (ii)

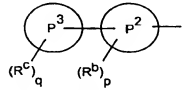
Group of formula (i)



(i)

where P^1 is phenyl, naphthyl, a 5 or 6 membered heteroaryl ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, a benzofused heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur, or a pyridofused heterocyclic ring containing 1 to 3 nitrogen atoms;
R^a is halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, CF_3, C_{1-6}alkoxy, OCF_3, hydroxy, cyano, nitro, hydroxyC_{1-6}alkyl, COC_{1-6}alkyl, CO_2R^5, SO_2R^5, NR^5R^6, $CONR^5R^6$, and $SO_2NR^5R^6$ where R^5 and R^6 are independently hydrogen or C_{1-6}alkyl;
n is 0, 1, 2 or 3;

Group of formula (ii)



(ii)

in which P^2 and P^3 are independently as defined for P^1 above;

R^b and R^c are independently as defined for R^a above;
p and q are independently as defined for n above;

L is a single bond or NH;
R^2 is hydrogen or together with the group R^3 forms a further group -CH = CH- or $(CR^7R^8)_2$- where R^7 and R^8 are independently hydrogen or C_{1-6}alkyl;
R^3 is hydrogen or together with R^2 forms a further group as defined above;
Y is N or CH;
X is N or CH;
R^4 is hydrogen or C_{1-6}alkyl.

2. A compound according to claim 1 in which Y is CH.

3. A compound according to claim 1 or 2 in which X is N.

4. A compound according to any of the preceding claims in which R^2 is hydrogen or together with R^3 forms a further group -$(CH_2)_2$-.

5. A compound according to any the preceding claims in which R^4 is a methyl group.

6. A compound according to any of the preceding claims in which R^1 is a group of formula (i) wherein P^1 is phenyl or oxazolyl.

7. A compound according to any one of claims 1 - 5 in which R^1 is a group of formula (ii) wherein P^2 is pyrazolyl and P^3 is phenyl.

8. A compound according to claim 1 which is a compound E1 - E89 (as described above) or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1 which is:
2,3-Dihydro-1-(5-methyl-1-phenylpyrazol-4-yl carbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,
1-(2-Fluorobenzoyl)-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,
1-[1-(4-cyanophenyl)-5-ethylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,
1-[1-(4-cyanophenyl)-5-methylpyrazol-4-ylcarbonyl]-2,3-dihydro-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-g]isoquinoline,

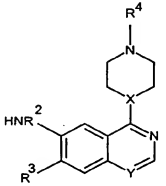
2,3-Dihydro-1-(4-ethyl-2-methyloxazol-5-ylcarbonyl)-8-(4-methylpiperazin-1-yl)pyrrolo[3,2-*g*]isoquinoline
or a pharmaceutically acceptable salt thereof.

10. A process for the preparation of a compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt which comprises either:

(a) when L is single bond, coupling a compound of formula (II)

(II)

in which R^1 is as defined in formula (I) and A is an activated carboxylic acid group with a compound of formula (III);



(III)

in which R^2, R^3, R^4, X and Y are as defined in formula (I); or

(b) where L is NH, coupling a compound of formula (IV)

(IV)

in which R^1 is as defined in formula (I) and B is either -N=C=O or is NH_2 in the presence an appropriate urea forming agent, with a compound of formula (III) as defined above;

and optionally thereafter for either process (a) or (b):

- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

11. A compound according to any of claims 1 to 9 for use in therapy.

12. A compound according to any of claims 1 to 9 for use in treatment of depression.

13. A pharmaceutical composition which comprises a compound according to any of claims 1 to 9 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

14. The use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders in which a ligand with affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is beneficial.

15. A method of treating diseases or disorders in which a ligand with affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors is beneficial which comprises administering a safe and therapeutically effective amount to a patient in need thereof of a compound according to one of claims 1 to 9 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/EP 00/10908

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/22 C07D401/12 C07D239/94 C07D471/04 A61K31/437
A61K31/47 A61K31/505 //(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data, EPO-Internal, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 50358 A (GASTER LARAMIE MARY ;RAMI HARSHAD KANTILAL (GB); WYMAN PAUL ADRIAN) 12 November 1998 (1998-11-12) cited in the application see whole document, especially definitions of D and Ra ---	1-15
Y	WO 98 47868 A (GASTER LARAMIE MARY ;WYMAN PAUL ADRIAN (GB); SMITHKLINE BEECHAM PL) 29 October 1998 (1998-10-29) cited in the application see general formula ---	1-15
Y	WO 99 31086 A (GASTER LARAMIE MARY ;SMITHKLINE BEECHAM PLC (GB)) 24 June 1999 (1999-06-24) cited in the application see general formula and examples --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2001	01 02 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. .ional Application No
PCT/EP 00/10908

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 00 06575 A (GASTER LARAMIE MARY ;HEIGHTMAN THOMAS DANIEL (GB); WYMAN PAUL ADRI) 10 February 2000 (2000-02-10) the whole document	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/10908

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ional Application No
PCT/EP 00/10908

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9850358 A	12-11-1998	AU 7431098 A	27-11-1998
		CN 1260781 T	19-07-2000
		EP 0975593 A	02-02-2000
		NO 995065 A	15-10-1999
		PL 336317 A	19-06-2000
WO 9847868 A	29-10-1998	NONE	
WO 9931086 A	24-06-1999	EP 1047691 A	02-11-2000
WO 0006575 A	10-02-2000	NONE	